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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Musty et al
Serial No.:	10/561,756
Confirmation No.:	1614
Filed:	December 21, 2005
For:	PHARMACEUTICAL COMPOSITIONS COMPRISING CANNABICHROMENE TYPE COMPOUNDS
Examiner:	Renee Claytor
Art Unit:	1617

Declaration of Brian Anthony Whittle Under 37 C.F.R. § 1.132

I, Brian Anthony Whittle, hereby declare the following:

1.1 I am a co-founder of GW Pharma and held the position of Scientific Director at GW Pharma from 1998 to 2008 when I retired. Prior to that I was a co-founder of a company which later became Phytopharm Plc and held the position of Chief Executive from 1990 to 1994 and Chief Scientific Officer from 1994 to 1998. Prior to that I was the Managing Director of Research Consultants (International) Limited, a subsidiary of Ethical Holdings plc. From 1981 to 1989, I founded and managed Brian Whittle Associates Limited, a pharmaceutical development consultancy. From 1979 to 1981 I was Director of Regulatory Affairs and Health Registration for Wyeth Europa Limited and from 1969 to 1979 I was Head of Pharmacology at Reckitt and Colman plc. From 1960 to 1969 I was Head of the Central Nervous Systems Unit at ICI Pharmaceuticals Limited. Prior to that I was a lecturer in Pharmacology at Sunderland University and a pharmacist at the Royal Marsden Hospital, London.

1.2 I am a Fellow of the Royal Pharmaceutical Society, The Linnean Society and previously a fellow of the British Institute of Regulatory Affairs. I have a B Pharm degree from the University of Nottingham in 1954, a PhC Diploma by the Pharmaceutical Society in 1954, an MSc by the University of London in 1957 and a PhD also by the University of London in 1964.

1.3 I have published extensively in the field of phyto-pharmaceuticals and am the named inventor on numerous patents in the field. I am knowledgeable in the areas of botanicals, pharmacology, and formulation. My curriculum vitae is attached as Appendix 1 hereto.

2. As a highly knowledgeable person in the field of phyto-pharmaceuticals, I make this declaration in support of the above referenced patent application.

3. I have reviewed the above-identified application, the Final Office Action for the above-identified application, and related documentation, and in particular the rejection of the claims as obvious (35 USC § 103) in view of Brooke et al (US6328992) and I am of the opinion that the examiner is mis-construing what the skilled person would conclude from reading Brooke et al. I further believe that any mis-construction may be the result of a common misconception that the terms "cannabis" (plant material) and "cannabinoids" (a group of compounds unique to the plant) are inter-changeable and that any benefits (or risks) associated with e.g. smoking the plant material are attributable solely to this group of some 60 cannabinoids, when the plant contains as many as 400 different compounds. In fact, the cannabinoids may account for only a small proportion of the compounds present in the plant.

4. In particular, I believe that the Examiner's statement on page 3 of the Office Action, regarding the teaching of Brooke et al,

"Therefore it would be obvious to a person of ordinary skill in the art that the active ingredients of cannabis are a useful treatment for a variety of disorders, which include mood disorders such as stress and/ or depression."

is INCORRECT, since not all of the individual compounds present in the plant (and there are many) will be active, and certainly any one compound will not be beneficial in treating all of the listed ailments. Indeed, the skilled person would most likely attribute the beneficial activities of "cannabis" to either THC and /or CBD. Furthermore, the "cannabinoid" mixture in the drug formulation disclosed in Brooke, is one representative of European cannabis, comprising approximately equal proportions of THC (33%), and CBD (35%) together with a break down product CBN (32%). There is no recorded CBC in the cannabinoid mixture in the drug formulation disclosed in Brooke et al.

5. Indeed I would go further to suggest that a person skilled in the art would, with respect to the indication "stress and depression", most likely attribute any effect to THC, the cannabinoid responsible for giving the user a "high", and would also be well aware that cannabis is also considered, by many, to be responsible for causing depression (particularly in teenage users) – see, for example, www.rcpsych.ac.uk/mentalhealthinfo/problems/alcoholanddrugs/cannabisandmentalhealth.aspx, such that there might be a prejudice against using any cannabinoid in the treatment of mood disorders.

6. Accordingly, the ordinary skilled person would NOT have been motivated by the teaching of Brooke et al to use cannabichromene to treat mood disorders. Indeed, it is more likely that reports linking cannabis with mental illness would have led the skilled person in other directions.

7.1 The Examiner also comments on the CBC content of cannabis plants, referring to the Vogelmann et al reference and the Rowan and Fairbairn reference. In particular, the Examiner states on page 3-4 of the Office Action: "Applicants contend that one would interpret that the medicinal uses of cannabis [described by Brooke] would not include CBC as a candidate compound to try for any medicinal indication."

7.2 I do not concur with this statement, as any cannabinoids **may** have a medicinal use. However, it is reasonable to conclude that a skilled person would have concentrated on the **primary cannabinoids** THC and CBD and NOT a minor cannabinoid, such as CBC, particularly given that CBC is only found in very small quantities in mature plants and it is use of "cannabis" from these mature flowering plants which provide the anecdotal evidence for many of its medicinal applications – (usually, but not always high THC varieties).

8. Indeed, both Vogelmann, and Rowan and Fairbairn, support the argument that CBC is NOT found in any significant amount (relative to e.g. THC or CBD) in such mature plants. The

opening two paragraphs of Rowan and Fairbairn discuss cannabis plants suggesting that there are two basic types: THC rich (drug type) and CBD rich (fibre type). The second paragraph suggests there may also be an "intermediate" type and one containing CBG monoethyl ether. (**It will be noted that there are no predominant CBC types.**) The examiner goes on to suggest that a "THC-rich race always possesses CBC sometimes in large amounts", and that "in some light situations there is a higher concentration of CBC compared to THC and CBG" and that "accordingly, there is no reason to expect that CBC would not have any medicinal purpose." Office Action at page 4. I address these points in the two paragraphs below:

9. Vogelmann makes it quite clear that, in the flowering plant, (and the cannabinoids predominate in the head) CBC is found in **relatively small** amounts (Table 1) 127μg CBC vs 3575μg THC! Indeed, in the discussion section it is suggested that there may be two pathways for cannabinoid formation, existing at **different stages** in plant development. That CBC predominates in early life, but rapidly gives way to THC in the adult plant, clearly supports the supposition that the skilled person would relate the benefits derived from the mature cannabis plant (and more particularly the flowering head) to one or more of the predominant constituents, rather than relatively minor constituents be that CBC, other minor cannabinoids present, or one or more of the many non-cannabinoid constituents of the plant (remembering, of course, that the cannabinoids only constitute a small proportion of the overall chemical make up.) It appears therefore that the examiner is taking a number of phrases out of context. Thus, the comment by the Examiner on page 4 of the Office Action that:

> "Vogelmann et al teaches that in some light situations there is a higher concentration of CBC compared to THC and CBG"

relates back to non-mature plant material and consequently the statement, and its relevance to "cannabis" (as it is used medicinally/ recreationally) is misleading. Table 1 of Vogelmann demonstrates this, and for example, the abstract makes it quite clear that "the cannabinoid profile of young seedlings differ significantly from that of adult plants."

10. Rowan and Fairbairn also make it quite clear that their work is conducted on 14 day old material. Thus, when the examiner states on page 4 of the Office Action that:

"the THC-rich race always possess CBC, sometimes in large amounts."
the sentence must be read in the context of the study undertaken, namely analysis of seedling material, NOT mature cannabis. Reference to table 2 shows that the combined CBC and CBD (not an ideal comparison) content in 14 day old seedlings and mature plants is radically different (means of 11.8:1.3; 4.46:0.6; and 9.4:trace)

11. Thus, in summary, it is my opinion that a skilled person, on reading Brooke, would:

a) not link the two distinct statements:

i) "several medicinal uses have been found for the **active ingredients** of cannabis, including the ingredients THC, CBN, CBD and CBC", and

ii) "the medicinal uses of **cannabis** include...list (1) to (10)"

(since the first relates to active ingredients, e.g. pure phyto cannabinoids or synthetic cannabinoids, and the second to uses of cannabis) together in the manner which the examiner does, to infer that each listed active ingredient, identified in sentence i), may be used to treat any indication (taught for cannabis) as identified in sentence ii).

b) have focused their attention on the major cannabinoids THC and CBD and would have been **dissuaded from looking at CBC** because it is a cannabinoid that does **NOT** generally prevail in **mature plants**, and it is the anecdotal uses of such **mature cannabis plants** which provides the necessary motivation. That cannabis plants are complex and may contain some 60 different cannabinoids, and over 400 compounds (see e.g. Turner page 1, column 2) supports this proposition; and

c) have been prejudiced against selecting CBC to, in particular, use as a medicine to treat mood disorders given the link between cannabis and depression, and would not have had a reasonable expectation of success in making or using the claimed invention. This argument is further supported by the fact that such medical indications are not suggested in Travis and Turner, which suggest uses for the "active ingredient" cannabichromene.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued there from.

Date: 26th November 2008

[Brian Anthony Whittle]